characteristics of an endogenous gene of a given cell line

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ASSIGNEE: Applied Research Systems*Ars Holding N.V., Curacao, Netherlands Antilles (foreign corp.)

APPL-NO: 07/893,447

DATE FILED: May 28, 1992

ART-UNIT: 184

PRIM-EXMR: Robert A. Wax

ASST-EXMR: Miguel Escallon

LEGAL-REP: Browdy and Neimark

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          5422 HOMOLOGOUS
          8035 RECOMBINAT?
L1         260 HOMOLOGOUS(W)RECOMBINAT?
=> s l1 and regulatory(2w)element?

          6302 REGULATORY
        762645 ELEMENT?

           220 REGULATORY(2W)ELEMENT?
L2          24 L1 AND REGULATORY(2W)ELEMENT?
=> s l2 and (exogenous or heterologous)
          2667 EXOGENOUS
          1676 HETEROLOGOUS
L3          19 L2 AND (EXOGENOUS OR HETEROLOGOUS)
=> s l3 and (exogenous or heterologous)(2w)regulatory(w)element?
          2667 EXOGENOUS
          1676 HETEROLOGOUS
          6302 REGULATORY

        762645 ELEMENT?
             1 (EXOGENOUS OR HETEROLOGOUS)(2W)REGULATORY(W)ELEMENT?
L4           0 L3 AND (EXOGENOUS OR HETEROLOGOUS)(2W)REGULATORY(W)ELEMENT?
=> s (exogenous or heterologous)(2w)regulatory(w)element?
          2667 EXOGENOUS
          1676 HETEROLOGOUS
          6302 REGULATORY

        762645 ELEMENT?
L5           1 (EXOGENOUS OR HETEROLOGOUS)(2W)REGULATORY(W)ELEMENT?
=> d l5 cit,ab

1.  5,242,812, Sep. 7, 1993, Method for production and purification of
hepatitis B vaccine; Zeev Even-Chen, 435/70.3; 424/88, 89; 435/69.3;
530/395, 412, 414, 415, 416, 417, 806; 935/65 [IMAGE AVAILABLE]

US PAT NO:     5,242,812 [IMAGE AVAILABLE]            L5: 1 of 1

ABSTRACT:
Processes are provided for producing purified, hepatitis B surface
antigen particles in mammalian cells which comprise culturing mammalian
cells which produce the particles in a culture medium supplemented with a
serum free of high molecular weight contaminant proteins and recovering
the purified, hepatitis B surface antigen particles.
Removal of molecules having a molecular weight greater than about
3.times.10.sup.5 daltons by prefractionation, for example, allows cells
to be grown in culture media containing high levels of fetal calf serum,
removes high molecular weight contaminant proteins which may be
inhibitory to cell growth and simplifies purification of HBsAg since high
molecular weight contaminant proteins are the major contaminants removed
by purification processes.
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the expression of proteolytically sensitive recombinant products. The isolation and characterization of additional genes from species of the genus Pichia is also described, as well as uses therefore.

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=> s l3 and amplifi?

        188041 AMPLIFI?
L6          60 L3 AND AMPLIFI?
=> wild(w)type?
'WILD(W)TYPE?' IS NOT A RECOGNIZED COMMAND
=> s l6 and wild(w)type?

          8105 WILD
       1262404 TYPE?

          1957 WILD(W)TYPE?
L7          41 L6 AND WILD(W)TYPE?
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=> d l7 1-41 cit
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1. 5,367,060, Nov. 22, 1994, Structure, production and use of heregulin; Richard L. Vandlen, et al., 530/399, 350 [IMAGE AVAILABLE]

2. 5,366,874, Nov. 22, 1994, Molecular cloning and expression of biologically-active diphtheria toxin receptor; Leon Eidels, et al., 435/69.1, 7.1, 7.2, 252.3, 320.1; 536/23.5 [IMAGE AVAILABLE]

3. 5,364,934, Nov. 15, 1994, Plasma carboxypeptidase; Dennis T. Drayna, et al., 536/23.2; 435/240.2, 252.3, 320.1 [IMAGE AVAILABLE]

4. 5,364,769, Nov. 15, 1994, Nucleic acid encoding neurotrophic factor four (NT-4), vectors, host cells and methods of production; Arnon Rosenthal, 435/69.1, 69.4, 240.1, 240.2, 320.1; 536/23.5, 23.51 [IMAGE AVAILABLE]

5. 5,350,671, Sep. 27, 1994, HCV immunoassays employing C domain antigens; Michael Houghton, et al., 435/5, 6, 975; 436/512, 518; 530/300, 326, 327, 328, 812, 826; 930/220, 223 [IMAGE AVAILABLE]

6. 5,348,886, Sep. 20, 1994, Method of producing recombinant eukaryotic viruses in bacteria; Stephen C. Lee, et al., 435/320.1, 69.1, 172.3, 252.3, 252.33; 536/23.1 [IMAGE AVAILABLE]

7. 5,346,991, Sep. 13, 1994, Tissue factor mutants useful for the treatment of myocardial infarction and coagulopathic disorders; Soumitra Roy, et al., 530/350; 435/172.3; 530/381, 829 [IMAGE AVAILABLE]

8. 5,338,665, Aug. 16, 1994, Peptide library and screening method; Peter J. Schatz, et al., 435/6, 7.32, 7.37, 172.3, 252.3, 252.33, 320.1; 935/73, 79, 80 [IMAGE AVAILABLE]

9. 5,324,663, Jun. 28, 1994, Methods and products for the synthesis of oligosaccharide structures on glycoproteins, glycolipids, or as free molecules, and for the isolation of cloned genetic sequences that determine these structures; John B. Lowe, 435/320.1, 69.1, 70.3, 172.3, 193, 240.2; 536/23.2; 935/14, 32, 70 [IMAGE AVAILABLE]

receptor; Gary L. Stiles, et al., 435/252.3, 69.1, 320.1; 536/23.5 [IMAGE AVAILABLE]

11. 5,316,931, May 31, 1994, Plant viral vectors having heterologous subgenomic **promoters** for systemic expression of foreign genes; Jon Donson, et al., 435/172.3, 69.1, 70.1, 320.1; 536/23.72, 24.1; 800/205; 935/25, 57, 64, 67 [IMAGE AVAILABLE]

12. 5,310,668, May 10, 1994, Varicella-zoster virus as a live recombinant vaccine; Ronald W. Ellis, et al., 424/199.1, 230.1; 435/172.3, 235.1, 320.1; 935/32, 57, 65 [IMAGE AVAILABLE]

13. 5,310,661, May 10, 1994, Nucleic acid encoding the .alpha. chain prodomains of inhibin and method for synthesizing polypeptides using such nucleic acid; Anthony J. Mason, et al., 435/69.1, 69.4, 240.2, 252.3, 320.1; 536/23.5, 23.51; 935/11 [IMAGE AVAILABLE]

14. 5,306,631, Apr. 26, 1994, Compositions and method for inhibition of HIV production; Gail Harrison, et al., 435/172.3, 240.2, 320.1; 935/56, 71 [IMAGE AVAILABLE]

15. 5,286,654, Feb. 15, 1994, Detection and purification of activin polypeptide; Edward T. Cox, et al., 436/501, 536; 530/388.22, 395, 413 [IMAGE AVAILABLE]

16. 5,262,177, Nov. 16, 1993, Recombinant viruses encoding the human melanoma-associated antigen; Joseph P. Brown, et al., 435/235.1; 424/185.1, 199.1, 232.1; 435/69.3, 172.3, 240.2, 252.3, 252.33, 320.1; 530/350; 536/23.5; 935/9, 32, 41, 57, 65, 70, 73 [IMAGE AVAILABLE]

17. 5,256,770, Oct. 26, 1993, Oxidation resistant thrombomodulin analogs; Charles B. Glaser, et al., 530/381; 435/69.6; 530/380 [IMAGE AVAILABLE]

18. 5,242,829, Sep. 7, 1993, Recombinant pseudorabies virus; Dennis L. Panicali, et al., 435/320.1; 424/199.1, 229.1, 232.1; 435/69.1, 69.3, 172.3 [IMAGE AVAILABLE]

19. 5,223,610, Jun. 29, 1993, Cholera toxin gene regulated by growth hormone **promoter**; Frank H. Burton, et al., 536/24.1; 435/69.2, 172.3, 320.1 [IMAGE AVAILABLE]

20. 5,223,408, Jun. 29, 1993, Method for making variant secreted proteins with altered properties; David V. Goeddel, et al., 435/69.3, 69.4, 69.52, 69.6, 69.7, 172.3, 189, 195, 215, 216, 226 [IMAGE AVAILABLE]

21. 5,216,126, Jun. 1, 1993, Receptor polypeptides and their production and uses; Edward T. Cox, et al., 530/350, 388.22, 389.1 [IMAGE AVAILABLE]

22. 5,215,893, Jun. 1, 1993, Nucleic acid encoding the ba chain prodomains of inhibin and method for synthesizing polypeptides using such nucleic acid; Anthony J. Mason, et al., 435/69.1, 69.4, 240.2, 252.3, 320.1; 536/23.5, 23.51; 935/11 [IMAGE AVAILABLE]

23. 5,206,161, Apr. 27, 1993, Human plasma carboxypeptidase B; Dennis T. Brown, et al., 435/212; 48.1 [IMAGE AVAILABLE]

24. 5,202,238, Apr. 13, 1993, Production of chimeric antibodies by **homologous** **recombination**; H. Perry Fell, Jr., et al., 435/69.6, 69.7, 70.1, 70.21, 172.3, 320.1; 530/387.3, 388.8; 536/23.53; 935/15, 111 [IMAGE AVAILABLE]

25. 5,198,346, Mar. 30, 1993, Generation and selection of novel DNA-binding proteins and polypeptides; Robert C. Ladner, et al., 435/69.1, 172.3, 252.3, 320.1 [IMAGE AVAILABLE]

26. 5,194,376, Mar. 16, 1993, Baculovirus expression system capable of producing foreign gene proteins at high levels; C. Yong Kang, 435/69.1; 204/180.1, 182.8, 299R; 435/172.3, 320.1 [IMAGE AVAILABLE]

27. 5,186,933, Feb. 16, 1993, Synthesis and immunogenicity of rotavirus genes using a baculovirus expression system; Mary K. Estes, 424/215.1;

435/172.1, 172.3, 235.1, 320.1; 530/826; 935/24, 32, 57, 65 [IMAGE AVAILABLE]

28. 5,180,675, Jan. 19, 1993, Recombinant fowlpox virus; Robert Drillien, et al., 435/235.1; 424/199.1, 232.1; 435/236, 320.1; 935/32 [IMAGE AVAILABLE]

29. 5,174,993, Dec. 29, 1992, Recombinant avipox virus and immunological use thereof; Enzo Paoletti, 424/199.1, 207.1, 210.1, 214.1, 222.1, 224.1, 231.1, 232.1; 435/235.1, 320.1; 935/32, 57, 65 [IMAGE AVAILABLE]

30. 5,141,742, Aug. 25, 1992, Vaccines against melanoma; Joseph P. Brown, et al., 424/186.1, 277.1; 435/69.3, 70.1, 71.1, 71.2; 530/350, 395; 536/23.5 [IMAGE AVAILABLE]

31. 5,098,837, Mar. 24, 1992, Macrolide biosynthetic genes for use in streptomyces and other organisms; Robert J. Beckmann, et al., 435/172.3, 71.2, 76, 91.41, 91.5, 169, 172.1, 252.35, 320.1, 886; 536/23.2, 23.7; 935/6, 9, 22, 29, 59, 60, 61, 66, 72, 75 [IMAGE AVAILABLE]

32. 5,093,258, Mar. 3, 1992, Recombinant fowlpox virus and recombination vector; Lawrence K. Cohen, et al., 435/235.1; 424/199.1, 232.1; 435/172.3, 320.1; 935/6, 32, 65 [IMAGE AVAILABLE]

33. 5,089,396, Feb. 18, 1992, Nucleic acid encoding .beta. chain prodomains of inhibin and method for synthesizing polypeptides using such nucleic acid; Anthony J. Mason, et al., 435/69.1, 69.4, 240.2, 252.3, 320.1; 536/23.51; 935/11 [IMAGE AVAILABLE]

34. 5,049,488, Sep. 17, 1991, Method and nucleic acid for the preparation of lecithin:cholesterol acyltransferase; Bradford W. Baer, et al., 435/6, 172.3, 803; 436/501; 530/397; 536/24.31; 935/78 [IMAGE AVAILABLE]

35. 5,041,379, Aug. 20, 1991, Heliothis expression systems; Malcolm J. Fraser, et al., 435/235.1, 69.1, 70.1, 172.3, 240.2, 320.1; 536/23.2, 23.6, 23.72; 935/3, 6, 9, 22, 33, 34, 47, 48, 59, 60, 61, 66, 70 [IMAGE AVAILABLE]

36. 5,030,576, Jul. 9, 1991, Receptors for efficient determination of

ligands and their antagonists or agonists; Thomas J. Dull, et al., 435/69.7; 69.1; 530/350, 388.22; 536/23.1, 24.i [IMAGE AVAILABLE]

37. 5,017,487, Mav 21, 199i, Vaccinia DNA; Hendrik G. Stunnenberg, et al., 435/172.3, 235.1, 320.1, 948; 536/24.i; 935/6, 32, 34, 57 [IMAGE AVAILABLE]

38. 4,920,209, Apr. 24, 1990, Oral vaccines; Alan R. Davis, et al., 435/235.1; 424/199.1, 227.1, 233.i; 435/69.3, 172.3 [IMAGE AVAILABLE]

39. 4,885,251, Dec. 5, 1989, Recombinant DNA expression vectors and DNA compounds which encode isopenicillin N synthetase; Thomas D. Ingolia, et al., 435/183, 172.3, 252.2, 252.3, 252.33, 252.35, 254.11, 254.5, 320.1; 536/23.2, 23.7; 935/14, 27, 34, 60, 68, 72 [IMAGE AVAILABLE]

40. 4,859,609, Aug. 22, 1989, Novel receptors for efficient

determination of ligands and their antagonists or agonists; Thomas J. Dull, et al., 436/501; 435/7.22, 7.3i, 7.9, 968; 436/63, 503, 537; 530/402, 806, 808; 935/8i, 109 [IMAGE AVAILABLE]

4i. 4,798,885, Jan. 17, 1989, Compositions of hormonally active human and porcine inhibin containing an .alpha. chain and 62 chain; Anthony J. Mason, et al., 530/350; 930/10, 260, DIG.530, DIG.821 [IMAGE AVAILABLE]

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L1            0 CHAPPEL, SCOTT/IN
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E1            1      CHAPPEL, LARRY R/IN
E2            5      CHAPPEL, RAYMOND M/IN
E3            0 --> CHAPPEL, SCOTT/IN
E4            6      CHAPPEL, SCOTT C/IN
E5            1      CHAPPEL, TIMOTHY M/IN
E6            3      CHAPPELEAR, ROBERT N/IN
E7            1      CHAPPELIE, NORMAN A/IN
E8            1      CHAPPELIE, NORMAN ANDREW/IN
E9            4      CHAPPELL, ALBERT R/IN
E10           1      CHAPPELL, ALICE M/IN
E11           3      CHAPPELL, ANTHONY G/IN
E12           2      CHAPPELL, AUSTIN/IN
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L2            6 "CHAPPEL, SCOTT C"/IN
=> d l2 1-6 cit

1.  5,352,779, Oct. 4, 1994, Site-directed mutagenesis modified DNA
encoding glycoprotein hormones and methods of use; **Scott C. Chappel**,
et al., 536/23.51; 435/69.1, 69.4, 252.3, 320.1; 530/399; 536/23.5 [IMAGE
AVAILABLE]

2.  5,272,071, Dec. 21, 1993, Method for the modification of the
expression characteristics of an endogenous gene of a given cell line;
**Scott C. Chappel**, 435/172.3, 69.1, 172.1, 252.3, 320.1; 536/23.1,
24.3; 935/6, 23, 34, 42 [IMAGE AVAILABLE]

3.  5,262,518, Nov. 16, 1993, Ovulation kit comprising FSH isoforms with
varying half-lives; **Scott C. Chappel**, 530/313; 435/975 [IMAGE
AVAILABLE]

4.  5,260,421, Nov. 9, 1993, Site-directed mutagenesis modified
glycoprotein hormones; **Scott C. Chappel**, et al., 530/397, 398, 399
[IMAGE AVAILABLE]

5.  5,240,832, Aug. 31, 1993, Heteropolymeric protein production methods;
Christie A. Kelton, et al., 435/69.4, 69.1, 172.3, 240.2, 320.1;
536/23.1, 23.5, 23.51; 930/110; 935/6, 13, 34, 60, 61, 66, 70 [IMAGE
AVAILABLE]

6.  5,087,615, Feb. 11, 1992, Novel method of ovulation induction in
humans; **Scott C. Chappel**, 514/21; 435/69.4; 514/12; 530/313, 324
[IMAGE AVAILABLE]
=> d l1 2 leg
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L1            0 SEA FILE=USPAT CHAPPEL, SCOTT/IN
=> d l2 2 leg


US PAT NO:     5,272,071 [IMAGE AVAILABLE]          L2: 2 of 6
DATE ISSUED:   Dec. 21, 1993
TITLE:         Method for the modification of the expression
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Processing
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          29185  SILENT
        5616614  GENE?
      S1    1544  SILENT(3W)GENE?
?s s1 and homologous(w)recombination

          1544  S1
        194232  HOMOLOGOUS
        161210  RECOMBINATION
         14283  HOMOLOGOUS(W)RECOMBINATION
      S2      13  S1 AND HOMOLOGOUS(W)RECOMBINATION
?rd s2

...completed examining records
      S3      10  RD S2 (unique items)
?t s3/6/1-10\

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 3/6/1     (Item 1 from file: 5)
10486906     BIOSIS Number: 96086906
  REARRANGEMENT OF SAPA HOMOLOGS WITH CONSERVED AND VARIABLE REGIONS IN
CAMPYLOBACTER-FETUS


 3/6/2     (Item 1 from file: 76)
1926733  82003576171
  Method for the modification of the expression characteristics of an
enoogenous gene of a given cell line


 3/6/3     (Item 1 from file: 434)
12505993   Genuine Article#: LR651   Number of References: 34
Title: USING SIMULTANEOUS, TANDEM GENE REPLACEMENTS TO STUDY EXPRESSION OF
    THE MULTICOPY UBIQUITIN-FUSION (FUS) GENE FAMILY OF TRYPANOSOMA-CRUZI
(Abstract Available)


 3/6/4     (Item 2 from file: 434)
11836719   Genuine Article#: JQ146   Number of References: 65
Title: THE RELAPSING FEVER AGENT BORRELIA-HERMSII HAS MULTIPLE COPIES OF
    ITS CHROMOSOME AND LINEAR PLASMIDS  (Abstract Available)
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3/6/5 (Item 3 from file: 434)
11518152 Genuine Article#: HN934 Number of References: 23

Title: TRANS-ACTING FACTORS AND PROPERLY POSITIONED DNA ELEMENTS REPRESS MATING-TYPE GENES IN FISSION YEAST (Abstract Available)

3/6/6 (Item 4 from file: 434)
11275465 Genuine Article#: GW053 Number of References: 58
Title: ONCOGENES RESULT IN GENOMIC ALTERATIONS THAT ACTIVATE A TRANSCRIPTIONALLY SILENT, DOMINANTLY SELECTABLE REPORTER GENE (NEO) (Abstract Available)

3/6/7 (Item 5 from file: 434)
10893241 Genuine Article#: FP319 Number of References: 48
Title: MODULATION OF GENE ACTIVITY BY CONSECUTIVE GENE TARGETING OF ONE CREATINE-KINASE M-ALLELE IN MOUSE EMBRYONIC STEM-CELLS (Abstract Available)

3/6/8 (Item 6 from file: 434)
10707719 Genuine Article#: FB733 Number of References: 25
Title: RECOMBINASE-MEDIATED GENE ACTIVATION AND SITE-SPECIFIC INTEGRATION IN MAMMALIAN-CELLS (Abstract Available)

3/6/9 (Item 7 from file: 434)
09450572 Genuine Article#: U3655 Number of References: 32
Title: THE NATURALLY-OCCURRING SILENT INVERTASE STRUCTURAL GENE SUC2-DEGREES CONTAINS AN AMBER STOP CODON THAT IS OCCASIONALLY READ THROUGH

3/6/10 (Item 8 from file: 434)
08452243 Genuine Article#: K9586 Number of References: 64
Title: REPLICATION AND SEGREGATION OF PLASMIDS CONTAINING CIS-ACTING REGULATORY SITES OF SILENT MATING-TYPE GENES IN SACCHAROMYCES-CEREVISIAE ARE CONTROLLED BY THE SIR GENES
?t s3/7/2,3,6,7,8

3/7/2 (Item 1 from file: 76)
DIALOG(R)File 76:Life Sciences Collection

1926733 82003576171
Method for the modification of the expression characteristics of an endogenous gene of a given cell line
Chappel, S.C.
Applied Res. Syst. Ars Holding N.V., Curacao (Netherlands Antilles)
Publ: 21 Dec 1993 1993
Patent No.: US Patent 5,272,071
Language: English
Document Type: Patent
Subfile: 33 Medical and Pharmaceutical Biotechnology Abstracts

A method of activating a predetermined normally transcriptionally silent gene within the genome of a cell line so as to enable said cell line to express the gene product of said gene, comprising inserting a DNA construct into said genome by homologous recombination, said DNA construct comprising a DNA regulatory segment capable of stimulating expression of said gene when operatively linked thereto and a DNA targeting segment homologous to a region of said genome within or proximal to said gene, wherein said construct is inserted such that said regulatory segment is operatively linked to said gene of interest.

3/7/3 (Item 1 from file: 434)
DIALOG(R)File 434:SciSearch(R)

12505993 Genuine Article#: LR651 Number of References: 34
Title: USING SIMULTANEOUS, TANDEM GENE REPLACEMENTS TO STUDY EXPRESSION OF THE MULTICOPY UBIQUITIN-FUSION (FUS) GENE FAMILY OF TRYPANOSOMA-CRUZI
Author(s): GILLESPIE RD; AJIOKA J; SWINDLE J
Corporate Source: UNIV TENNESSEE CTR HLTH SCI,DEPT MICROBIOL & IMMUNOL,858 MADISON AVE/MEMPHIS//TN/38163; UNIV TENNESSEE CTR HLTH SCI,DEPT MICROBIOL & IMMUNOL,858 MADISON AVE/MEMPHIS//TN/38163
Journal: MOLECULAR AND BIOCHEMICAL PARASITOLOGY, 1993, V60, N2 (AUG), P 281-292
ISSN: 0166-6851
Language: ENGLISH Document Type: ARTICLE
Abstract: Many genes in trypanosomes exist as members of multicopy gene families. Due to this fact it is frequently difficult to determine if specific members of a gene family are expressed. We describe here a strategy for simultaneous tandem gene replacement in T cruzi which leads to the replacement of the gene of interest by a silent reporter gene, the expression of which can be assayed in stable transformants. To determine if the FUS1 gene (one of 5 copies of the ubiquitin-fusion, FUS, gene family) was expressed, stable G418-resistant transformants were isolated in which the tandemly arrayed CUB2.65 and FUS1 genes were precisely replaced by the neomycin phosphotransferase (neo(r)) and chloramphenicol acetyltransferase (CAT) genes, respectively. All stable clones carrying the tandem gene replacements were shown to express the CAT activity indicating that FUS1 is expressed in mid-log epimastigotes. Northern blot analysis of parasites carrying the tandem gene replacements indicated that at least one other member of the FUS gene family is expressed and that there were no apparent polar effects on the expression of genes downstream of the replacement events. These experiments have demonstrated the utility of tandem gene replacements as a means of inserting a nonselected reporter gene into the chromosome, facilitating the molecular genetic analysis of the expression of multicopy gene families.

3/7/6 (Item 4 from file: 434)
DIALOG(R)File 434:SciSearch(R)

11275465 Genuine Article#: GW053 Number of References: 58
Title: ONCOGENES RESULT IN GENOMIC ALTERATIONS THAT ACTIVATE A TRANSCRIPTIONALLY SILENT, DOMINANTLY SELECTABLE REPORTER GENE (NEO)

102390

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          6175 HOMOLOGOUS
          8576 RECOMBINATION
L1         366 HOMOLOGOUS(3W)RECOMBINATION
=> s l1 and promoter?
         20762 PROMOTER?
L2         325 L1 AND PROMOTER?
=> s l2 and eukaryotic(3w)cell?

          2088 EUKARYOTIC
        286683 CELL?
          1263 EUKARYOTIC(3W)CELL?
L3          88 L2 AND EUKARYOTIC(3W)CELL?
=> s l3 and endogenous(w)target(w)gene?
          5224 ENDOGENOUS
         67961 TARGET

       1052864 GENE?

             1 ENDOGENOUS(W)TARGET(W)GENE?
L4           0 L3 AND ENDOGENOUS(W)TARGET(W)GENE?
=> s endogenous(w)target(w)gene?
          5224 ENDOGENOUS
         67961 TARGET

       1052864 GENE?

L5           1 ENDOGENOUS(W)TARGET(W)GENE?
=> d l5 cit,ab

1.  5,324,660, Jun. 28, 1994, Genes which influence Pichia proteolytic
activity, and uses therefor; Martin A. Gleeson, et al., 435/254.23, 69.1,
938 [IMAGE AVAILABLE]

US PAT NO:     5,324,660 [IMAGE AVAILABLE]            L5: 1 of 1

ABSTRACT:
The isolation and characterization of genes involved in proteolytic
processing in species of the genus Pichia is described. The availability
of such genes has enabled the generation of strains of Pichia which are
deficient in proteolytic activity, which strains are useful as hosts for
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Author(s): DREWS RE; CHAN VW; SCHNITZER LE
Corporate Source: HARVARD UNIV,BETH ISRAEL HOSP,CHARLES A DANA RES INST/BOSTON//MA/02215; HARVARD UNIV,BETH ISRAEL HOSP,THORNDIKE LAB/BOSTON//MA/02215; BETH ISRAEL HOSP,DEPT MED/BOSTON//MA/02215; HARVARD UNIV,SCH MED/BOSTON//MA/02115
Journal: MOLECULAR AND CELLULAR BIOLOGY, 1992, V12, N1 (JAN), P198-206
Language: ENGLISH Document Type: ARTICLE
Abstract: Although oncogenes and tumor suppressor genes have been implicated in carcinogenesis and tumor progression, their relationship to the development of genomic instability has not been elucidated. To examine this role, we transfected oncogenes (polyomavirus middle [Py] and large T [MT and LT]) and adenovirus serotype 5 E1A) into two NIH 3T3-derived cell lines, EN/NIH 2-4 and EN/NIH 2-20. Both cell lines contain two stable integrants of a variant of the retrovirus vector pZipNeoSV (x)1 that has been modified by deletion of the enhancer elements from the long terminal repeats. DNA rearrangements activating the silent neomycin phosphotransferase gene (neo) present in these integrants were identified by selection of cells in the antibiotic G418. Whereas control-transfected EN/NIH cell lines do not yield G418-resistant subclones (GRSs), a fraction of oncogene-transfected EN/NIH 2-4 (8 of 19 Py MT, 5 of 17 Py LT, and 11 of 19 E1A) and 2-20 (7 of 15 Py MT) cell lines gave rise to GRSs at differing frequencies (0.33 x 10(-6) to 46 x 10(-6) for line 2-4 versus 0.11 x 10(-6) to 1.3 x 10(-6) for line 2-20) independent of cell generation time. In contrast, a distinctly smaller fraction of mutant Py MT-transfected EN/NIH cell lines (1 of 10 MT23, 1 of 10 MT1015, and 0 of 10 MT59b) resulted in GRSs. Southern analysis of DNA from selected oncogene-transfected GRSs demonstrated genomic rearrangements of neo-containing cellular DNA that varied in type (amplification and/or novel fragments) and frequency depending on the specific oncogene and EN/NIH cell line used in transfection. Furthermore, only one of the two neo-containing genomic loci present in both EN/NIH cell lines appeared to be involved in these genomic events. In addition to effects related to the genomic locus, these observations support a role for oncogenes in the development of genetic changes associated with tumor progression.

3/7/7 (Item 5 from file: 434)
DIALOG(R)File 434:SciSearch(R)

10[illegible]241 Genuine Article#: FP319 Number of References: 48
Title: MODULATION OF GENE ACTIVITY BY CONSECUTIVE GENE TARGETING OF ONE CREATINE-KINASE M-ALLELE IN MOUSE EMBRYONIC STEM-CELLS
Author(s): VANDEURSEN J; LOVELLBADGE R; OERLEMANS F; SCHEPENS J; WIERINGA B
Corporate Source: CATHOLIC UNIV NIJMEGEN,DEPT CELL BIOL & HISTOL,POB 9101/6500 HB NIJMEGEN//NETHERLANDS/; CATHOLIC UNIV NIJMEGEN,DEPT CELL BIOL & HISTOL,POB 9101/6500 HB NIJMEGEN//NETHERLANDS/; NATL INST MED RES,EUKARYOT MOLEC GENET LAB/LONDON NW7 1AA//ENGLAND/
Journal: NUCLEIC ACIDS RESEARCH, 1991, V19, N10, P2637-2643
Language: ENGLISH Document Type: ARTICLE
Abstract: The cytosolic creatine kinases (CK's; EC 2.7.3.2) BB, BM and MM are dimeric isoenzymes which have an important role in energy metabolism and display characteristic tissue- and stage-specific patterns of expression in mammals. To study the functional role of the

distribution of the CK isoenzymes we have focussed on the modulation of expression of the genes encoding the individual B and M subunits, starting at the muscle creatine kinase (CKM) gene which is

transcriptionally inactive during early embryogenesis. Using repeated rounds of gene targeting in mouse embryonic stem (ES) cells, two types of mutant cell lines were obtained. First, we generated a cell line in which insertion of a neomycin resistance (neo(r)) gene had disrupted one of the CKM alleles. Subsequently, from this cell line, following introduction of an insertion type vector designed for replacement of the muscle specific CKM-enhancer by the constitutively acting polyoma virus enhancer PyF441, several independent doubly targeted clones were isolated which all had insertions in the previously neo-disrupted CKM allele. In some of these ES clones, the targeted enhancer replacement resulted in gene correction and functional activation of the silent CKM gene. Dimerisation between the ectopically expressed CKM subunits and CKB subunits which are normally present at high levels in ES cells, led to the formation of the BM isoform of CK in these clones.

3/7/8 (Item 6 from file: 434)
DIALOG(R)File 434:SciSearch(R)

10707719 Genuine Article#: FB733 Number of References: 25
Title: RECOMBINASE-MEDIATED GENE ACTIVATION AND SITE-SPECIFIC INTEGRATION IN MAMMALIAN-CELLS
Author(s): OGORMAN S; FOX DT; WAHL GM
Corporate Source: SALK INST BIOL STUDIES,GENE EXPRESS LAB/LA JOLLA//CA/92037
Journal: SCIENCE, 1991, V251, N4999, P1351-1355
Language: ENGLISH Document Type: ARTICLE
Abstract: A binary system for gene activation and site-specific integration, based on the conditional recombination of transfected sequences mediated by the FLP recombinase from yeast, was implemented in mammalian cells. In several cell lines, FLP rapidly and precisely recombined copies of its specific target sequence to activate an otherwise silent beta-galactosidase reporter gene. Clones of marked cells were generated by excisional recombination within a chromosomally integrated copy of the silent reporter. By the reverse reaction, integration of transfected DNA was targeted to a specific chromosomal site. The results suggest that FLP could be used to mosaically activate or inactivate transgenes for analysis of vertebrate development, and to efficiently integrate transfected DNA at predetermined chromosomal locations.
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L1      1060763 GENE?
      s l1 and (silent or transcription?(2w)inactiv

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=> s l1 and (silent or transcriotion?(2w)inactiv?)
          6021 SILENT
          4170 TRANSCRIPTION?
         62500 INACTIV?
            16 TRANSCRIPTION?(2W)INACTIV?

L2         4610 L1 AND (SILENT OR TRANSCRIPTION?(2W)INACTIV?)
=> s l2 and homologous(2w)recombin?tion
          6257 HOMOLOGOUS
         21705 RECOMBIN?
           388 HOMOLOGOUS(2W)RECOMBIN?
L3          49 L2 AND HOMOLOGOUS(2W)RECOMBIN?
=> s l3 and regulatory(w)sequence?

          7294 REGULATORY
        256755 SEQUENCE?
           579 REGULATORY(W)SEQUENCE?
L4          11 L3 AND REGULATORY(W)SEQUENCE?
=> d l4 1-11 cit,ab

1.  5,350,671, Sep. 27, 1994, HCV immunoassays employing C domain
antigens; Michael Houghton, et al., 435/5, 6, 975; 436/512, 518; 530/300,
326, 327, 328, 812, 826; 930/220, 223 [IMAGE AVAILABLE]

US PAT NO:     5,350,671 [IMAGE AVAILABLE]            L4: 1 of 11

ABSTRACT:
Immunoassays for the detection of antibodies to HCV are provided which
employ "C" domain antigens. Immunoassay kits comprising such antigens are
also provided.

2.  5,272,071, Dec. 21, 1993, Method for the modification of the
expression characteristics of an endogenous **gene** of a given cell
line; Scott C. Chappel, 435/172.3, 69.1, 172.1, 252.3, 320.1; 536/23.1,
24.3; 935/6, 23, 34, 42 [IMAGE AVAILABLE]

US PAT NO:     5,272,071 [IMAGE AVAILABLE]            L4: 2 of 11

ABSTRACT:

 Normally transcriptionally **silent** **genes** in a cell line or
microorganism may be activated for expression by inserting a DNA
regulatory element which is capable of promoting the expression of a
normally expressed **gene** product in that cell or which is promiscuous,
the regulatory element being inserted so as to be operatively linked with
the normally **silent** **gene** in question. The insertion is
accomplished by means of **homologous** **recombination** by creating a
DNA construct including a segment having a DNA segment of the normally
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silent **gene** (targeting DNA) and the DNA regulatory element to induce **gene** transcription. The technique is also used to modify the expression characteristics of any endogenous **gene** of a given cell

line or microorganism.

3. 5,262,177, Nov. 16, 1993, Recombinant viruses encoding the human melanoma-associated antigen; Joseph P. Brown, et al., 435/235.1; 424/185.1, 199.1, 232.1; 435/69.3, 172.3, 240.2, 252.3, 252.33, 320.1; 530/350; 536/23.5; 935/9, 32, 41, 57, 65, 70, 73 [IMAGE AVAILABLE]

US PAT NO: 5,262,177 [IMAGE AVAILABLE] L4: 3 of 11

ABSTRACT:
Peptides or proteins related to a melanoma associated antigen are described. These are produced in large quantities via recombinant DNA techniques and/or by chemical synthetic methods. The peptides or proteins can be used as immunogens in vaccine formulations which can induce an immune response that selectively destroys melanoma cells in a vaccinated individual. Where the peptides or proteins are expressed by a recombinant virus, inactivated or live virus vaccine formulations may be prepared.

4. 5,223,254, Jun. 29, 1993, Respiratory syncytial virus: vaccines; Peter R. Paradiso, et al., 424/186.1, 211.1; 514/2, 8, 12 [IMAGE AVAILABLE]

US PAT NO: 5,223,254 [IMAGE AVAILABLE] L4: 4 of 11

ABSTRACT:
Polypeptides, nucleotides, and compositions useful for preparing diagnostic reagents for and vaccines against human Respiratory Syncytial Virus are disclosed. The polypeptides include short polypeptides which are related to a neutralizing and fusion epitope of the Respiratory Syncytial Virus fusion protein or a neutralizing epitope of the G protein.

5. 5,198,346, Mar. 30, 1993, **Generation** and selection of novel DNA-binding proteins and polypeptides; Robert C. Ladner, et al., 435/69.1, 172.3, 252.3, 320.1 [IMAGE AVAILABLE]

US PAT NO: 5,198,346 [IMAGE AVAILABLE] L4: 5 of 11

ABSTRACT:
Novel DNA-binding proteins, especially repressors of **gene** expression, are obtained by variegation of **genes** encoding known binding proteins and selection for proteins binding the desired target DNA sequence. A novel selection vector may be used to reduce artifacts. Heterooligomeric proteins which bind to a target DNA sequence which need not be palindromic are obtained by a variety of methods, e.g., variegation to obtain proteins binding symmetrized forms of the half-targets and heterodimerization to obtain a protein binding the entire asymmetric target.

6. 5,196,338, Mar. 23, 1993, Recombinant vectors for Haemophilus influenzae peptides and proteins; Algis Anilionis, et al., 435/252.3, 69.1, 69.7, 320.1; 530/350 [IMAGE AVAILABLE]

US PAT NO: 5,196,338 [IMAGE AVAILABLE] L4: 6 of 11

ABSTRACT:

Peptides and proteins related to an epitope comprising an outer membrane protein of Haemophilus influenzae are described. The peptides and proteins can be prepared by methods including novel and improved methods of purification from H. influenzae cultures, and by recombinant DNA and chemical synthetic techniques. Additionally, recombinant vectors containing nucleotide sequences encoding PBOMP-1 and PBOMP-2 related peptides, proteins and fusion proteins are also described. Recombinant vectors include plasmid DNA and viral DNA such as human viruses, animal viruses, insect viruses and bacteriophages that direct the expression of the PBOMP-1 and PBOMP-2 related peptides, proteins, and fusion proteins in appropriate host cells. The peptides, proteins, fusion proteins and viruses both "live" and "inactivated" are used as immunogens in vaccine formulations to protect against H. influenzae infections. The peptides, proteins and fusion proteins are also used as reagents in immunoassays as well as to prepare immunoglobulins for passive immunization. Use of the nucleotide sequences encoding the PBOMP related peptides, proteins and fusion proteins in hybridization assays is also described.

7. 5,196,316, Mar. 23, 1993, Enzyme and DNA coding therefor; Yasuno Iwasaki, et al., 435/69.1, 68.1, 219, 232, 320.1; 530/350, 855; 536/23.2 [IMAGE AVAILABLE]

US PAT NO: 5,196,316 [IMAGE AVAILABLE] L4: 7 of 11

ABSTRACT:
The invention concerns a peptidylhydroxyglycine N-C lyase (PHL) catalyzing the reaction

R-GlyOH.fwdarw.R-NH.sub.2
wherein R represents a peptide residue, and GlyOH represents an .alpha.-hydroxyglycine residue linked to the C-terminus of said peptide R by an amide bond, a recombinant DNA molecule coding for a PHL, a method for the preparation of such a recombinant DNA molecule, processes for the preparation of PHL from a natural source or by means of the said recombinant DNA molecule, and the use of PHL for the preparation of an amidated peptide R-NH.sub.2.

8. 5,141,742, Aug. 25, 1992, Vaccines against melanoma; Joseph P. Brown, et al., 424/186.1, 277.1; 435/69.3, 70.1, 71.1, 71.2; 530/350, 395; 536/23.5 [IMAGE AVAILABLE]

US PAT NO: 5,141,742 [IMAGE AVAILABLE] L4: 8 of 11

ABSTRACT:
Peptides or proteins related to a melanoma associated antigen are described. These are produced in large quantities via recombinant DNA techniques and/or by chemical synthetic methods. The peptides or proteins can be used as immunogens in vaccine formulations which can induce an immune response that selectively destroys melanoma cells in a vaccinated individual. Where the peptides or proteins are expressed by a recombinant virus, inactivated or live virus vaccine formulations may be prepared.

9. 5,110,908, May 5, 1992, Haemophilus influenzae peptides and proteins;

Robert A. Deich, et al., 530/403; 435/71.1, 71.2, 187, 189, 193, 172.3; 820. 851; 530/333, 345, 350, 806, 808, 825 [IMAGE AVAILABLE]

US PAT NO: 5,110,908 [IMAGE AVAILABLE] L4: 9 of 11

ABSTRACT:
Peptides and proteins related to an epitope comprising an outer membrane protein of Haemophilus influenzae are described. The peptides and proteins can be prepared by methods including novel and improved methods of purification from H. influenzae cultures, and by recombinant DNA and chemical synthetic techniques. Additionally, recombinant vectors containing nucleotide sequences encoding PBOMP-1 and PBOMP-2 related peptides and proteins are also described. Recombinant vectors include plasmid DNA and viral DNA such as human viruses, animal viruses, insect viruses and bacteriophages that direct the expression of the PBOMP-1 and PBOMP-2 related peptides and proteins in appropriate host cells. The peptides, proteins and viruses both "live" and "inactivated" are used as immunogens in vaccine formulations to protect against H. influenzae infections. The peptides and proteins are also used as reagents in immunoassays as well as to prepare immunoglobulins for passive immunization. Use of the nucleotide sequences encoding the PBOMP related peptides and proteins in hybridization assays is also described.

10. 5,108,744, Apr. 28, 1992, Vaccines for Haemophilus influenzae; Robert A. Deich, et al., 424/190.1, 256.1; 514/2; 530/350, 403 [IMAGE AVAILABLE]

US PAT NO: 5,108,744 [IMAGE AVAILABLE] L4: 10 of 11

ABSTRACT:
Peptides and proteins related to an epitope comprising an outer membrane protein of Haemophilus influenzae are described. The peptides and proteins can be prepared by methods includng novel and improved methods of purification from H. influenzae cultures, and by recombinant DNA and chemical synthetic techniques. Additionally, recombinant vectors containing nucleotide sequence encoding PBOMP-1 and PBOMP-2 related peptides and proteins are also described. Recombinant vectors include plasmid DNA and viral DNA such as human viruses, animal viruses, insect viruses and bacteriophages that direct the expression of the PBOMP-1 and PBOMP-2 related peptides and proteins in appropriate host cells. The peptides, proteins and viruses both "live" and "inactivated" are used as immunogens in vaccine formulations to protect against H. influenzae infections. The peptides and proteins are also used as reagents in immunoassays as well as to prepare immunoglobulins for passive immunization. Use of the nucleotide sequences encoding the PBOMP related peptides and proteins in hybridization assays is also described.

11. 5,098,997, Mar. 24, 1992, Vaccines for Haemophilus influenzae; Algis Anilionis, et al.. 530/350; 435/69.3, 69.7, 851; 530/405, 806, 825 [IMAGE AVAILABLE]

US PAT NO: 5,098,997 [IMAGE AVAILABLE] L4: 11 of 11

ABSTRACT:
Peptides and proteins related to an epitope comprising an outer membrane protein of Haemophilus influenzae are described. The peptides and

proteins can be prepared by methods including novel and improved methods of purification from H. influenzae cultures, and by recombinant DNA and chemical synthetic techniques. Additionally, recombinant vectors

containing nucleotide sequences encoding PBOMP-1 and PBOMP-2 related peptides, proteins and fusion proteins are also described. Recombinant vectors include plasmid DNA and viral DNA such as human viruses, animal viruses, insect viruses and bacteriophages that direct the expression of the PBOMP-1 and PBOMP-2 related peptides, proteins, and fusion proteins in appropriate host cells. The peptides, proteins, fusion proteins and viruses both "live" and "inactivated" are used as immunogens in vaccine formulations to protect against H. influenzae infections. The peptides, proteins and fusion proteins are also used as reagents in immunoassays as well as to prepare immunoglobulins for passive immunization. Use of the nucleotide sequences encoding the PBOMP related peptides, proteins and fusion proteins in hybridization assays is also described.

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        7089 HOMOLOGOUS
        9380 RECOMBINATION
         482 HOMOLOGOUS(W)RECOMBINATION
L2         1 L1 AND HOMOLOGOUS(W)RECOMBINATION
=> d l1 cit,ab

1.  5,468,615, Nov. 21, 1995, Binding assay employing a synthetic gene
for D4 dopamine receptors; Christopher L. Chio, et al., 435/7.2, 6, 69.1;
436/501; 536/23.5 [IMAGE AVAILABLE]

US PAT NO:     5,468,615 [IMAGE AVAILABLE]            L1: 1 of 5

ABSTRACT:
A modified gene coding for the human D4 dopamine receptor has been
synthesized by chemo-enzymatic methods. The nucleotide sequence of the D4
dopamine receptor gene was oh:raged to reduce the G+C content and to
eliminate intronic sequences, while maintaining the published amino acid
sequence. Using gene splicing by overlap extension and PCR amplification
of long oligonucleotides (>200 bases), 3 synthetic fragments of about 400
base pairs each were amplified, from which the full length gene was
assembled. Stable expression of this gene has been achieved in CHO-K1
cells, using an inducible expression system, and in HEK293 cells.
=> d l2 kwic

US PAT NO:     5,468,615 [IMAGE AVAILABLE]            L2: 1 of 1

DRAWING DESC:

DRWD(8)

 FIG. 4. Scatchard analysis of (.sup.3 H)-spiperone binding in **HEK**
**293** D4-24 cells.

DRAWING DESC:

DRWD(10)

 FIG. 5. Stable expression of D4 receptors in **HEK** **293** D4-24
cells.

DRAWING DESC:

DRWD(11)

 .sup.3 H-spiperone binding at 540 pM was determined in membranes
prepared from **HEK** **293** D4-24 cells harvested at the indicated
passage.

DETDESC:
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